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FLORENCE KALTOVICH, REGULATORY REVIEW OFFICER

FROM: GEORGE MILLS, M.D., CO-CHAIRMAN, NR-LU-10 PLA COMMITTEE

ITEM: CLINICAL REVIEW OF NR-LU-10 PLA SUBMISSION

DATE: SEPTEMBER 7, 1994

ORIGINAL

PLA 94-308

TITLE: [redacted] for the Preparation of Murine Monoclonal Antibody NR-LU-10 Fab for Technetium Tc-99m Imaging of Small Cell Lung Cancer

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Volumes - 37

Pivotal Phase III Clinical Trial (BB-IND 2633)

Objectives of the Phase III Clinical Trial

Primary Objective: Estimation of the accuracy of staging patients with newly diagnosed small cell lung cancer.

End Point of Primary Objective:

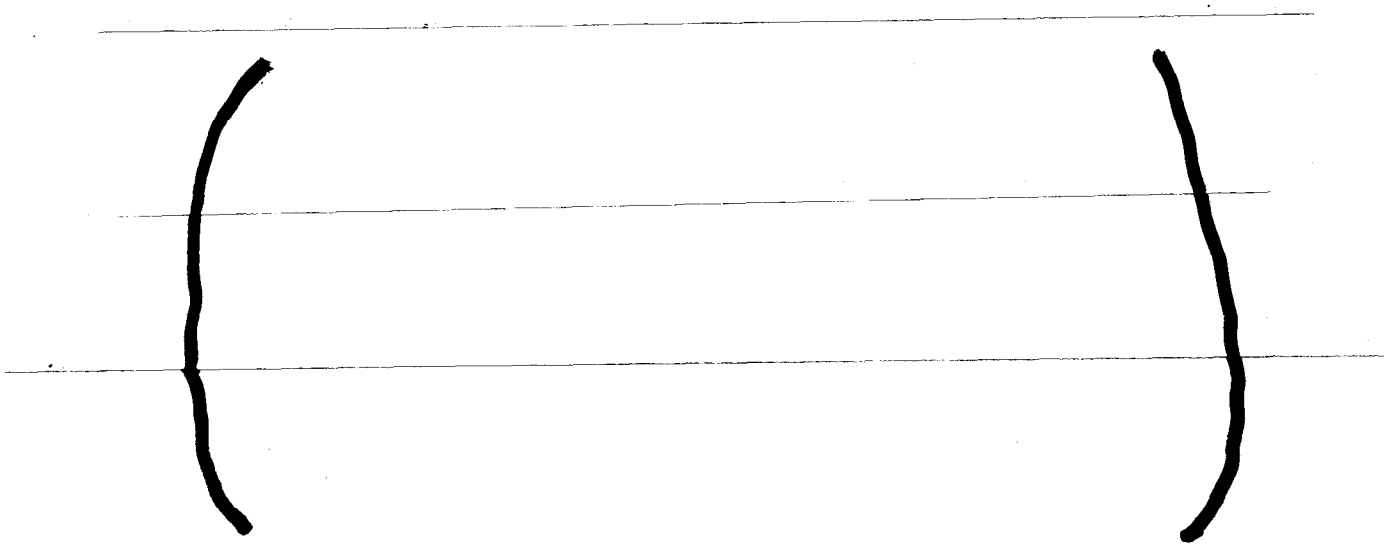
Stratification of patients in the trial into two groups:

Limited Disease

Extensive Disease

Secondary Objectives:

1. The evaluation of safety of Murine Monoclonal Antibody NR-LU-10 Fab for Technetium Tc-99m Imaging of Small Cell Lung Cancer
2. Estimation of sensitivity and positive predicted value of NR-LU-10 imaging
3. The comparison of NR-LU-10 to standard diagnostic modalities



The indication supported from the findings of the Phase III Clinical Trial for the use of **NR-LU-10-Tc 99m** [redacted] is for the use of **NR-LU-10 imaging** for the **primary staging of patients** with **newly-diagnosed small cell lung cancer to stage patients** into the two established treatment groups:

1. **Extensive Disease**

2. **Limited Disease.**

Based upon the stage of the patient's disease, a physician must decide between recommending potentially curative, but toxic, combined modality therapy that adds chest radiation to combination chemotherapy for patients with limited disease or palliative combination chemotherapy alone for patients with extensive disease.

Patients who are identified as Extensive Disease by NR-LU-10 **would not** have to **complete the standard diagnostic modalities.**

Patients who are identified as Limited Disease by NR-LU-10 **would** have to **complete the standard diagnostic modalities** currently utilized to stage SCLC

The Standard Diagnostic Modalities for Staging SCLC

CT of chest

CT of brain

CT of Abdomen/Liver

Nuclear Medicine Bone Scan

Bone Marrow Biopsy/Aspiration.

Patient Eligibility for The Phase III Trial

nonpregnant adults

new, histologically-confirmed diagnosis of small cell lung cancer

at least one known evaluable lesion

patients had not received prior to study entry:

chemotherapy

radiation therapy

any other investigational agent for this tumor

Patient Prestudy Evaluation

physical examination

x-ray or CT of the chest

CT of the head

CT of the abdomen

nuclear medicine bone scan

bone marrow aspiration

Patient Demographics of Submitted Patients

96 Patients

77% male

Average age 61 years (range 32-88 years)

56% of patients had extensive disease

42% of patients had limited disease

Product administered

5-10 mg NR-LU-10 Fab labeled with 15-30 mCi Tc 99m pertecnetate

diluted to 30 ml in normal saline

Intravenous injection over 3-5 minutes

A cathartic was administered to attempt to purge radionuclide from the intestines prior to imaging.

Imaging procedure for the Phase III Trial

14-17 hours post injection

Planar gamma camera images

Regional and/or whole body

SPECT tomographic images of the chest

Imaging Technique

general purpose collimator

The energy window was 15% centered at 140 keV or on the full width at half the maximum of the photopeak.

Planar imaging was begun with an anterior thorax view with the abdomen shielded with a lead apron to the level of the xiphoid to obtain 500,000 total counts.

Planar acquisition times of 8-10 minutes were expected, and a maximum of 10 minutes was suggested if count rates were low. All subsequent survey views were collected for the same length of time as used for the first anterior thorax view.

SPECT imaging was performed using a 360 degree rotation around the thorax with 64 stops.

SPECT Images were formatted on a 64X64 matrix and were reconstructed in the transverse, saggital and coronal views using 2 pixel width slices.

TIME SEQUENCE OF EVENTS FOR THE IND AND PLA SUBMISSIONS

The pivotal Phase III clinical trial for IND 2633 was initiated on August 24, 1988.

The Phase III, multicenter clinical trial was conducted at 23 sites in the United States and one site in Denmark.

A planned interim analysis occurred after 44 patients. On August 17, 1989 [redacted] met with CBER to discuss the results of the interim analysis. It was agreed for [redacted] to proceed with the second stage of patient accrual but to analyze and present the staging results from all patients together without stratification into Limited Disease or Extensive Disease.

The [redacted] was filed on [redacted] with 96 patients, 89 of whom were evaluable. [redacted] submitted a [redacted] for the manufacture of NR-LU-10 bulk antibody in [redacted]

Following the submission of the PLA, several clinical sites remained open to patient accrual to explore secondary objectives of the study:

1. determining the usefulness of restaging patients after receiving therapy

2. the influence of chemotherapy on the development of an antiglobulin response.

In August 1990, the study was closed to new patient entry.

Total patient accrual was the following:

TOTAL = 173 patients

173 patients received the first antibody administration/imaging procedure

66 patients of the 173 patients received a second administration/imaging procedure

Bioequivalence data for BI production of the NR-LU-10 to compare to the [redacted] NR-LU-10 was submitted to the [redacted] on September 20, 1993.

[redacted] was [redacted] due to the change in manufacturing from [redacted] to Boehringer Ingelheim. The PLA submitted by Boehringer Ingelheim (PLA #94-308) is a modification of the [redacted]

Clinical Background on Diagnosis and Staging of Small Cell Lung Cancer

Small cell lung cancer (SCLC) accounts for 20% of all lung cancers, with approximately 30,000 new cases annually in the United States. Micrometastases are present at the time of diagnosis in virtually all patients. If not treated, the disease spreads widely and death occurs within a few months.

Despite the nearly universal presence of micrometastases in these patients, there are significant differences in prognosis and the recommended treatment that depend on whether distant, detectable metastases are present, "Extensive Disease", or whether detectable tumor is confined to one hemithorax, the mediastinum, and ipsilateral supraclavicular lymph nodes, "Limited Disease."

Accurate staging of newly-diagnosed small cell lung cancer is indicated to determine prognosis and to facilitate appropriate therapeutic decisions.

Primary surgical treatment with curative intent is rarely a therapeutic option in patients with small cell lung cancer, even among those with Limited Disease. Instead, the importance of distinguishing Limited from Extensive Disease small cell lung cancer involves differences in prognosis and choice of medical therapy.

The major goals of therapy for patients with Extensive Disease are palliation and prolongation of survival using intensive combination chemotherapy. Cure may be a reasonable goal for care of patients with limited disease but requires a more toxic and costly treatment strategy that adds chest radiation to intensive combination chemotherapy.

Chest radiation therapy plus combination chemotherapy is associated with increased risks of bone marrow suppression, painful, debilitation and/or life-threatening esophageal, pulmonary and cardiac toxicity. In addition bone marrow suppression and consequent infectious complications are more severe when chest radiation is added to combination chemotherapy.

"Limited Disease" is a diagnosis of exclusion: a patient has limited disease only if no evidence of Extensive Disease has been found. Adding tests that can detect different subsets of metastatic disease, therefore, would be expected to improve the accuracy of a diagnosis of exclusion. By contrast, once any single test indicates extensive disease, no further testing improves the accuracy of staging of SCLC.

Extensive Disease Outcome When Treated

25% of patients achieve complete remission

median survival is 33 weeks

1-3% of patients survive more than 3 years

Limited Disease Outcome When Treated

60% of patients achieve complete remission

median survival exceeds one year

15-25% long term survival

The advantages of radiotherapy to the involved hemithorax for the Limited Disease group are the following:

to control and prevent local recurrence

a small but definite benefit in survival statistics

1-4 months of additional length of survival

an increase from 5% to 15% for the total surviving population at two years

External beam radiation therapy has significant morbidity with decreased cardiac function, esophageal radiation injury and diminished pulmonary reserve. Mortality from the external beam radiation therapy is as high as 1%.

Patients with Extensive Disease that have received external beam radiation therapy to the involved hemithorax have had no change in length of survival but have sustained the expected increased morbidity and mortality.

The use of NR-LU-10 Fab labeled with Technetium Tc-99m has the potential to detect the primary and metastatic disease of SCLC with a single "First Best" test. The radiolabeled antibody may be detectable throughout the body and demonstrate widespread disease in multiple organs and anatomic sites rather than the currently requires multiple standard diagnostic modalities.

The distribution of potential small cell lung cancer metastatic sites for NR-LU-10 scan detection are the following:

lung

mediastinal lymph nodes

supraclavicular lymph nodes

pleura

liver

brain

bone

bone marrow

Sponsor's Summary of the Clinical Trial Findings

NR-LU-10 Imaging identified 82-86% of the patients on the study who had Extensive Disease with a positive predictive value of 95-100%. NR-LU-10 imaging alone was nearly as sensitive as the entire standard battery of tests in establishing the diagnosis of Extensive Disease small cell lung cancer.

NR-LU-10 Imaging identified 38-43% of all small cell lung cancer patients as not "Extensive Disease". The standard battery of tests identified 33-39%.

NR-LU-10 Imaging "understaged" as Limited Disease 9-11% of patients and the standard battery "understaged" 5-9% of patients, who had Extensive Disease.

NR-LU-10 Imaging "upstaged" to Extensive Disease 4-7% of 37 (11-19%) patients classified as Limited Disease by the standard battery of test.

In this subset of patients for the clinical trial, the accuracy of establishing a diagnosis of Limited Disease small cell cancer was improved over either NR-LU-10 imaging or the standard battery of tests by using both together.

A computer model of the data submitted by the sponsor predicts that the rate of "understaging" is reduced to near zero when the standard battery of tests is added to NR-LU-10 imaging.

A NR-LU-10 imaging is the best test to establish the diagnosis of Extensive Disease small cell lung cancer. The 45-48 patients on this study identified by NR-LU-10 imaging to have Extensive Disease could have begun treatment with combination chemotherapy immediately, thereby avoiding the costs, inconvenience, and discomfort of additional tests as well as the acute toxicities, morbidity, and costs of chest radiation, which would only be useful for patients with limited disease.

Addition of NR-LU-10 imaging to the standard battery of tests in the patients on this study "upstaged" to Extensive Disease 4-7 of 37 patients (11-19%) who had been classified originally as Limited Disease by the standard battery of tests. Accurately staging these patients allowed them to be presented the option of toxic but potentially curative therapy.

Of the patients in this study classified as Limited Disease by the standard battery of test, 11-19% were upstaged to Extensive Disease by adding NR-LU-10 imaging.

Based upon the finding from the Phase III Clinical Trial, the Sponsor has proposed the following Package Insert Information:

Sponsor's Proposed Package Insert (Synopsis)

Indications and Usage

[redacted] *is indicated for the primary staging of patients with small cell lung cancer. It establishes a diagnosis of extensive disease with a predictive value of 95-100%. For those patients with no evidence of extensive disease by NR-LU-10 imaging, it establishes a diagnosis of limited disease with a predictive value of 69-76%; the accuracy of establishing a diagnosis of limited disease can be improved by the addition of other tests, including chest x-ray, bone scan, CT examinations of the head and abdomen, and bone marrow aspirates and/or biopsies.*

[redacted] *is not indicated for differential diagnosis of suspected lung tumors because it has been shown in patient images also to localize to nonsmall cell lung cancer and carcinomas of the breast, ovary, colorectum, prostate, kidney, and liver.*

Imaging of patients revealed accumulation of radioactivity in the following normal sites: gall bladder, intestine, kidneys, urinary bladder, testes, midline nasal area, pituitary gland, salivary glands and the thyroid. Radioactivity also may appear to accumulate in other non-tumor areas such as regions of inflammation, increased vascular pool or recent surgical areas.

Description:

[redacted], *is a Kit for the Preparation of Murine Monoclonal Antibody NR-LU-10 Fab for the Technetium Tc 99m Imaging of Small Cell Lung Cancer. The* [redacted] *is used to prepare a technetium Tc 99m labeled murine monoclonal antibody Fab intended for intravenous administration for diagnostic use.* [redacted] *provides all the sterile, and pyrogen-free non-radioactive components needed for reaction with sterile, pyrogen-free sodium pertecnetate Tc 99m. Each Kit contains sufficient material to prepare one patient dose. Each Kit contains 1 vial of murine monoclonal antibody Fab; the contents of the vial containing the Fab fragment of NR-LU-10 are to be radiolabeled with technetium Tc 99m and administered to the patient. The Fab is derived from the enzymatic digestion of a purified IgG2b murine immunoglobulin directed against an approximately 40 kD glycoprotein carcinoma associated antigen. The antigen is expressed on small cell lung cancer, nonsmall cell lung cancer and many other epithelial tumors, including adenocarcinomas of the colon, breast, ovary, pancreas and prostate. Each vial contains 10 mg of Murine Monoclonal Antibody NR-LU-10 Fab in 1.0 ml o sterile, non-pyrogenic, Phosphate-Buffered Saline.*

Clinical pharmacology:

Following intravenous injection, technetium Tc 99m radiolabeled Murine Monoclonal Antibody NR-LU-10 Fab is rapidly cleared from the circulation with a mean half-life of 1.46 hours. Renal clearance is the primary route of elimination with 67.7% (SD 14.9%) of the injected dose of radiolabeled Murine Monoclonal Antibody NR-LU-10 Fab eliminated within the first 20-22 hours after administration. The secondary route of elimination is through the hepatobiliary system. There is, therefore, accumulation of radioactivity in the kidney, urinary bladder, gall bladder, and intestines. In addition, there may be localization of the radioactivity in the testes, midline nasal area, salivary glands, pituitary gland and the thyroid. In vitro data reveal no evidence of transfer of technetium Tc 99m to serum proteins.

Analysis and Review of the Scan Interpretation Method of the NR-LU-10 Phase III Clinical Trial

In this clinical trial, prior to the NR-LU-10 scan, the participating oncologist diagramed on the case report form all known lesions identified by the standard diagnostic modalities.

At the clinical site, the first Nuclear Medicine physician recorded, on the same case report form utilized by the participating oncologist, the NR-LU-10 scan detection of the previously known lesions from the standard diagnostic modalities and indicated any previously unsuspected lesions that were observed in the NR-LU-10 scans.

A second Nuclear Medicine physician read the NR-LU-10 scans "blinded" and recorded the lesions identified by NR-LU-10 on the case report forms.

The first and second interpretations were compared and if there was a discrepancy, the lesions in question were reviewed by a third Nuclear Medicine physician, who recorded his agreement or disagreement on the case report form.

The scan interpretations presented for the Phase III clinical trial results are the consensus of these reviews.

The indication for the use of NR-LU-10 in this clinical trial is as a **"first best" study to replace the standard diagnostic modalities** for patients with Extensive Disease. For a clinical trial of a "first best" scan, the interpretation of the NR-LU-10 scans should be blinded to the findings of the standard diagnostic modalities it is proposed to replace.

In review of this clinical trial, the findings of the standard diagnostic modalities were known to the first Nuclear Medicine physician when the "unblinded" interpretation of the scan was performed.

The second Nuclear Medicine physician was stated to be "blinded" when rendering the "blinded" interpretation. However, a comparison between the first and second interpretation results occurred at this time and there was potential to "unblind" the results of the first Nuclear Medicine physican's interpretation prematurely to the second Nuclear Medicine physician.

When a disparity in findings occurred between the first Nuclear Medicine physician's "unblinded" interpretation and the second Nuclear Medicine physician's "blinded" interpretation, the selected areas of disputed interpretation were indicated on the whole body diagram which identified all agreed and disputed lesions. Therefore, the first Nuclear Medicine physician's "unblinded" findings and the "blinded" findings of the second Nuclear Medicine physician were known to the third Nuclear Medicine physician [redacted]. This method allowed the

third Nuclear Medicine physician to see all "agreed" lesions and pointed out the possible, but disputed lesion(s). The third Nuclear Medicine physician interpreted the selected, "pointed out" regions of disputed interpretation only. The final consensus scan interpretation included all lesions as positive that were identified by two of three Nuclear Medicine physicians, two of whom were not blinded. The consensus interpretation of the NR-LU-10 scans was not a "blinded" interpretation and it is not appropriate for any Nuclear Medicine image interpretation to "point out" potential lesions. By pointing out the questionable areas, bias was introduced for every questionable lesion interpretation.

Therefore, the method utilized to render the final consensus interpretation of the scans must be considered unblinded and subject to bias.

In summary of the method utilized:

The **first** evaluation was performed at the clinical site by the experienced nuclear medicine physician who had full knowledge of the patient's clinical status and all of the standard diagnostic evaluations results as provided on the diagram by the participating oncologist.

The **second** interpretation of all scintiscans , termed a "blinded review", was performed by randomly dividing the scintiscans from all investigational sites between two nuclear medicine physicians who were consultants to [redacted] The second interpreter recorded the findings on a separate case report form.

If the interpretation of the first two Nuclear Medicine physicians were in agreement, the results were termed the consensus interpretation.

When there was a discrepancy between the first and second evaluation a **limited third interpretation of the specific sites of interpretation disagreement** was preformed to "break the tie".

the images were reviewed by the alternate nuclear medicine consultant to [redacted] who provided a third opinion, termed a "blinded review" for the specific areas of disagreement between the two primary interpreters. The third interpreter was provided a diagram of all lesions identified and a line drawn to the areas of question between the first two interpreters.

The potential for the introduction of bias and a lack of a true "blinded interpretation" is apparent in this scan interpretation methodology. To confirm if bias was introduced by this interpretation scheme, [redacted]

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Comments on the Clinical Trial Findings

The clinical trial evaluated NR-LU-10-Tc-99m as follows:

1. To stage patients to Limited or Extensive Disease as compared to standard diagnostic modalities.

To accomplish this, the radiolabeled antibody scan must detect the presence of metastatic disease, but not all organs involved nor also metastatic sites. The Sponsor has put forth the justification and indication that NR-LU-10-Tc 99m can replace the standard diagnostic modalities when the radiolabeled antibody scan demonstrates Extensive Disease. This will reduce the time, expense and discomfort of these test, states the sponsor.

Whole body NR-LU-10 scans for staging for patients with Extensive Disease has a high probability to correlate with standard diagnostic modalities since detection of only one lesion outside the involved hemithorax will result in the classification of Extensive Disease.

The Sponsor's concluded that the diagnosis of Extensive Disease by NR-LU-10 imaging could allow treatment with combination chemotherapy to begin immediately. This would avoid the costs, inconvenience, and discomfort of additional tests as well as the acute toxicities, morbidity, and costs of chest radiation, which would only be useful for patients with limited disease. This conclusion does not acknowledge any individual organ system's need for high sensitivity and high specificity detection for changes in the treatment plan.

The sponsor states patients with Limited Disease should be evaluated by NR-LU-10 and by the current standard diagnostic modalities. The value in staging the Limited Disease population with NR-LU-10 and the standard diagnostic modalities is the identification of the 5% of patients who should be in the Extensive Disease classification but are classified Limited Disease by the standard diagnostic modalities. In theory, this improved classification would spare these patients the potential morbidity and mortality of external beam radiation therapy. However, no improved outcome can be established or confirmed for these patients by this new classification with this diagnostic study.

2. To detect individual organ involvement.

The standard diagnostic modalities include CT examinations of the brain, chest, and liver/abdomen. It is well documented that the detection of anatomical changes of metastatic disease are superior by CT examination as compared to

standard Nuclear Medicine imaging. This limitation of anatomical detection is size dependent. CT images 0.5 cm lesions versus Nuclear Medicine imaging detecting 1.0- 2.0 cm lesions as a minimum routine lesion size.

Nuclear medicine whole body imaging for Tc-99m detection is limited by lesion size whether the radionuclide is an antibody or not. Lesions less than 2 cm in size are considered low potential for detection, while lesions greater than 2 cm are considered high potential for detection.

The findings of lesion size detection in this study are consistent with the known limitations of the state of the art in Nuclear Medicine Imaging.

Lesions < 1 cm - detection = 33%

Lesions 1-3 cm - detection = 55%

Lesions > 3 cm - detection = 85%

Nuclear Medicine imaging is also limited in the number of lesions detected. The potential to "hide or obscure" lesions with nuclear medicine planar imaging is a significant detection limitation as compared to CT imaging with multiple tomographic levels. To replace the individual standard diagnostic modalities, the radiolabeled antibody scan must detect involvement of the organ systems at approximately the same rate as the standard diagnostic modality.

The total number of involved organs among the study population was 274. 212 involved organs were detected by NR-LU-10 for a sensitivity of 77%. However, certain organ systems demonstrated a low sensitivity for detection of metastatic disease.

At the time of initial diagnosis, 17% of patients with SCLC have metastatic disease to the brain and 30% of all patients will develop metastatic disease to the brain prior to death. When metastatic disease to the brain is detected, external beam radiation therapy is indicated to reduce morbidity from the metastatic disease. There were 12 patients with metastatic disease to the brain. The radiolabeled antibody detected only 4 (sensitivity = 33%). Therefore, when the radiolabeled antibody study is negative for metastatic disease to the brain, CT imaging of the brain must be performed.

For liver involvement, 27 patients had metastatic disease and the radiolabeled antibody detected 20, sensitivity = 74%. This sensitivity is lower than standard nuclear medicine liver/spleen scanning and well below sensitivity for CT imaging of the liver. Other abdominal metastatic sites were known in 14 patients but only one was identified by NR-LU-10, sensitivity = 7%. Therefore, CT imaging of the liver/abdomen would continue to be performed for many

patients.

For SCLC involving lung and mediastinal/supraclavicular nodes, the detection sensitivity is greater than 88%. However, NR-LU-10 imaging, if approved, will not be available for readministration. Therefore, the assessment of tumor burden and response to therapy that are now accomplished by CT of the chest will continue to be performed in many cases.

3. To detect individual lesions within organs.

The standard diagnostic modalities include CT examinations of the brain, chest, and liver/abdomen. It is well documented that the detection of anatomical changes of metastatic disease are superior by CT examination as compared to Nuclear Medicine imaging. This limitation of anatomical detection is size dependent with CT imaging at 0.5 cm versus Nuclear Medicine limited to 1.0-2.0 cm lesions as a minimum routine lesion with Tc-99m. This limitation is number dependent with planar whole body imaging as compared to CT imaging which displays multiple tomographic levels. The potential to "hide or obscure" lesions with nuclear medicine planar imaging is a significant limitation as compared to CT imaging. To replace the individual standard diagnostic modalities, the radiolabeled antibody scan must detect lesions at approximately the same rate as the standard diagnostic modality. For individual lesions within organs, the radiolabeled antibody scan is severely limited in its ability to detect all lesions.

Evaluation of detection of multiple lesions within organs noted the sensitivity of 54% of 152 lesions within the skeleton. This would not appear to be adequate to remove the bone scan from the standard diagnostic modalities. 24 lesions within brain yielded only a 25% sensitivity and 43 lesions within the liver were detected with a sensitivity of 70%. With these sensitivities, the continued use of CT for brain and liver to determine tumor mass and response to therapy appears indicated. NR-LU-10 does not appear adequate to replace bone scans.

In summary, the sponsor has elected to limit the request for licensure to staging only. The integrated functions of organ and lesion detection must be evaluated and information on these limitations as compared to the standard diagnostic modalities must be defined in the package insert, if the request for licensure is approved.

The sponsor has elected to not pursue the readministration indication for NR-LU-10 even though 63 patients have received a second administration and scan in the trial. Without readministration imaging, the usefulness of the NR-LU-10 scan as a first best study is severely limited. The bulk of the primary tumor and the bulk of the metastatic disease as well as their response to chemotherapy is based on the initial workup findings and the comparison to the findings of the followup restaging. Without

readministration, the use of some or all of the standard diagnostic modalities will be required for patients who have Extensive or Limited Disease to assess the response to chemotherapy.

ANALYSIS AND REVIEW OF THE CLINICAL TRIAL FOR CONFIRMATION OF NR-LU-10 SCAN FINDINGS

The sponsor stated a lesion seen on the NR-LU-10 scans was a "positive" if two of the three reviewers identifies the lesion as positive. 124 lesions were identified by NR-LU-10 that were not seen by the standard diagnostic modalities. However, upon review, 26 of these 124 NR-LU-10 lesions that were unconfirmed lesions by the standard diagnostic modalities (21%) were identified by only one Nuclear Medicine physician and not identified or confirmed by the other two Nuclear Medicine physicians

NR-LU-10 scans detected disease in 38 organs which were not seen with the standard diagnostic modalities. Only 12 of these findings were confirmed.

In this clinical trial, the sponsor was not required to provide biopsy confirmation, clinical follow-up, or later standard diagnostic modality findings to confirm these unconfirmed lesions seen by NR-LU-10.

All lesions identified by the NR-LU-10 scan, that are not identified by the standard diagnostic modalities, should be confirmed by biopsy, followup standard diagnostic modality confirmation, and/or autopsy findings.

In the submitted data set of this clinical trial, a "positive is a positive" and with no biopsy confirmation required, the potential false positive findings are not able to be identified in this trial.

Analyis and Evaluation of Clinical Stage

37 patients entered the study with the clinical diagnosis of Limited Disease and 52 patients entered with the clinical diagnosis of Extensive Disease based on the standard battery of noninvasive diagnostic imaging tests. This distribution is reasonably similar to the reported proportion of Limited and Extensive Disease with the general population of patients with small cell lung cancer: 31% Limited and 69% Extensive Disease.

In some patients NR-LU-10 imaging suggested a change in clinical stage from that identified by the standard battery of tests.

Re-evaluation using accepted diagnostic modalities, including information from other procedures and the patients's clinical course, indicated that in some patients the presumed clinical stage based on the standard battery of tests was incorrect at the

time of entry into the study.

By defining a "true" stage based on this final assessment, NR-LU-10 imaging and the standard battery of test can each be scored independently for accuracy of staging.

In cases where a discrepancy between the standard evaluation and the NR-LU-10 imaging results could not be resolved, alternate assumptions of truth were made to yield lower and upper estimates of the accuracy of staging for each.

For example, when NR-LU-10 imaging identified a lesion that could alter stage, but that conventional tests and follow-up could not corroborate, the case was classified as an unresolved discrepancy. The upper limits of accuracy for standard stage and the lower limits for NR-LU-10 imaging stage are obtained by assuming standard stage to be correct in all these cases; The opposite assumption produces the upper limit of accuracy for NR-LU-10 imaging and the lower for the standard battery.

These cases of unresolved discrepancy should be resolved by review of the clinical followup, autopsy findings or followup standard diagnostic modalities.The use of alternate assumptions of truth should be eliminated in this clinical with a small patient population.

Safety Results

96 patients received the NR-LU-10 imaging agent.

There were no unexpected adverse reactions directly related to the use of this product. There were three minor events reported that were possibly related to the administration of the imaging agent:

- two patients had temperatures of 100.2 one hour after infusion of the antibody

- one patient developed facial urticaria approximately six hours after infusion of the antibody, shortly after receiving a cathartic.

Blood chemistry on 87 patients noted the following:

One patient developed elevated serum lipase, rising from 134 to 231 IU/L

Two patients developed elevated serum amylase, rising from 36 to 217 IU/L and from 135 to 203 IU/L.

These enzyme changes were not associated with any clinical symptoms. The values returned to normal by the time follow-up blood samples were obtained.

There were an additional 8 patients whose serum amylase rose, who were also asymptomatic, but on whom no follow-up is available to document return to baseline. Four of these patients had abnormal serum amylase prior to the study.

There were five patients who experienced elevations in serum lipase. They were also asymptomatic, and no information is available to determine if they returned to baseline. Three of these patients also had rises in serum amylase.

The possibility of NR-LU-10 interacting with the thyroid is noted by other reviewers and should be explored. Toxicity from Tc-99m should not be a consideration in the further evaluation. Tc-99m has been used for years to scan the thyroid and no suggestion of toxicity has been reported. In addition, the concern of the interaction by the antibody should be tempered by the shortened lifespan of the proposed patient population.

Antiglobulin Response

53 patients were evaluated with an ELISA assay

Serial serum samples were obtained on each patient for six months

Antiglobulin was elevated in three patients. The elevations were transient in two patients and sustained in one patient.

Evaluation of the NR-LU-10 scan Imaging

The quality of imaging submitted is appropriate and adequate for interpretation.

The biodistribution of the radiolabeled antibody is consistent throughout the studies.

The target to non-target is adequate in the thorax but the abdomen presents significant non-target activity in the hepatobiliary system, bowel, and urinary tract. Adjunctive imaging, e.g. CT or MRI scans, of abdominal structures will be clinically indicated.

NR-LU-10 localization in normal anatomical structures which may present "false positive" interpretations to the uninformed observer

Cross reactivity of NR-LU-10 for other tissues - **in vivo**

thyroid

anterior pituitary

salivary glands

testes

Route of Clearance

Kidney - ureter - bladder

Liver - gall bladder - small bowel - large bowel

Radiation Dosimetry

The Tc-99m radiolabel at a dose range of 15 - 30 mCi is appropriate to all NRC regulatory guidelines and is consistent with standard practice of diagnostic Nuclear Medicine.

The Whole body dose is 0.4 Rad and presents no safety concern.

The target organ for maximum radiation exposure is the kidney and it receive 4.23 rad/30 mCi. This is within acceptable limits and consistent with Tc 99m radionuclide administration and the primary radioisotope clearance route through the kidney with secondary clearance through the hepatobiliary system.

The dosimetry calculations are adequate and appropriate for this radioisotope. The clearance pattern of the radiolabled Fab fragment presents no unusual pattern of localization or clearance.

Concluding Comments

The image quality of the NR-LU-10 scans is good for evaluation of the thorax. The evaluation of the abdomen and liver will be marginal for this radiolabeled antibody due to the high nontarget activity in the hepatobiliary system, liver, kidneys and bowel.

The low sensitivity of lesion detection in the brain and the abdomen will limit the independent use of NR-LU-10 scans.

Without readministration, NR-LU-10 scans will not be utilized for evaluation of response to chemotherapy and restaging.

The lack of the complete submission of the 77 patients completed after the [redacted] submission is a concern. 63 of these patients were readministered NR-LU-10. The possibility that the outcome of the first administration scans and/or the readministered scans for these 77 patients were not favorable can not be ruled out. In support of this concern is the lack of pursuit of secondary objectives of the [redacted]

A Jul 11, 1994 telecor [redacted] with Dr. David Brill, Boehringer Ingelheim's U.S. agent, requested clarification and supporting information for the PLA. Dr. Brill assured Ms. Kaltovich that the information would be forth coming within a few weeks. A mid-August followup by Ms. Kaltovich noted an assurance that the information would arrive by the last week of August. To the current date, no information has been received.

CONCLUSIONS

The PLA submission, PLA 94-308, as submitted is not approvable.

The scan interpretations submitted from the clinical trial are consensus interpretations with an unblinded Nuclear Medicine physician who had full knowledge of the findings of all standard diagnostic modalities. This method of NR-LU-10-Tc-99m scan review does not provide a "blinded" consensus interpretation required for the NR-LU-10 imaging indication as a "first best" study to replace the standard diagnostic modalities. The NR-LU-10 scan interpretations must be preformed in a controlled and fully blinded manner to be able to assess the correlation with the standard diagnostic modalities. A reanalysis of the NR-LU-10 scans must be completed and submitted in support of the PLA.

The blinded scan interpretations must identify all involved organs and describe all lesions to correlate with the findings of the standard diagnostic modalities. All sites of apparent disease identified by NR-LU-10 that are not seen by the standard diagnostic modalities must be confirmed by clinical followup, later standard diagnostic modality or by biopsy. For patients to "upstaged" by NR-LU-10 imaging in the reanalysis, the new lesion(s)/organs must be documented by biopsy, additional standard imaging and/or clinical followup.

Source documents for all standard diagnostic modalities reports must be submitted. Confirmation of positive NR-LU-10 findings that are not contained in the standard diagnostic modality reports must be supported by source documents.

The 89 evaluable patients that have been submitted is a very limited study size. 77 additional patients were imaged in this clinical trial that have not been submitted with complete or audited clinical data. These patients should be fully audited and included in the reanalysis.

It is noted in the current data set from the submission that the detection of metastatic disease in the brain and extrahepatic abdomen is very low (sensitivity in brain of 25% and in abdomen of 7%). The reanalysis must address the need for standard diagnostic modalities to support NR-LU-10.

A July 11, 1994 telecon [redacted] with Dr. David Brill, Boehringer Ingelheim's U.S. agent, requested clarification and supporting information for the PLA. Dr. Brill assured Ms. Kaltovich that the information would be forth coming within a few weeks. A mid-August follow up by Ms. Kaltovich noted an assurance that the information would arrive by the last week of August. To the current date, no information has been received. (addendum - The response to the questions was received for my review on October 7, 1994. The following conclusions reflect the review of the submitted responses.)

CONCLUSIONS

The PLA submission, PLA 94-308, as submitted is not approved.

The scan interpretations submitted from the clinical trial are consensus interpretations with an unblinded Nuclear Medicine physician who had full knowledge of the findings of all standard diagnostic modalities. This method of NR-LU-10-Tc-99m scan review does not provide a "blinded" consensus interpretation required for the NR-LU-10 imaging indication as a "first best" study to replace the standard diagnostic modalities. The NR-LU-10 scan interpretations must be preformed in a controlled and fully blinded manner to be able to assess the correlation with the standard diagnostic modalities. A reanalysis of the NR-LU-10 scans must be completed and submitted in support of the PLA 94-0308.

The blinded scan interpretations must identify all involved organs and describe all lesions identified by NR-LU-10 imaging to correlate with the findings of the standard diagnostic modalities for each patient. All sites of apparent disease identified by NR-LU-10 that are not seen by the standard diagnostic modalities must be confirmed by clinical follow up, later standard diagnostic modality or by biopsy. For patients to be "upstaged" by NR-LU-10 imaging in the reanalysis, the new lesion(s)/organs must be documented by biopsy, additional standard imaging and/or clinical follow up.

For the reanalysis, false positive upstaging as extensive disease by NR-LU-10 imaging must be fully documented in the reanalysis. The specific lesions and/or organs incorrectly classified must be categorized for the false positive upstaged patients.

TO: T. E. BULL, PH.D., C0-CHAIRMAN, NR-LU-10 PLA COMMITTEE
FLORENCE KALTOVICH, REGULATORY REVIEW OFFICER

FROM: GEORGE MILLS, M.D. , C0-CHAIRMAN, NR-LU-10 PLA COMMITTEE

ITEM: ADDENDUM TO CLINICAL REVIEW OF NR-LU-10, BOEHRINGER INGELHEIM PLA 94-0308 SUBMISSION DATED: SEPTEMBER 7, 1994

DATE: OCTOBER 21, 1994

Since submitting the clinical review for the above listed PLA, the responses to the Telecon of July 11, 1994 were received for review on October 7, 1994. The Sponsor's responses to the submitted questions were consistent with the expected responses. There are no substantive changes in the conclusions of the clinical review.

I have updated the final paragraph of the review and the conclusions. Attached is the revised final paragraph of the review reflecting the receipt of the answers to the telecon and the amplified conclusions, based on the Sponsor's responses to the Telecon's questions.

For the reanalysis, false negative understaging as limited disease by NR-LU-10 imaging must be fully documented in the reanalysis. The specific lesions and/or organs incorrectly classified must be categorized for the false negative understaged patients.

For the reanalysis, false positive upstaging as extensive disease by standard diagnostic imaging must be fully documented in the reanalysis. The specific lesions and/or organs incorrectly classified must be categorized for the false positive upstaged patients.

For the reanalysis, false negative understaging as limited disease by standard diagnostic imaging must be fully documented in the reanalysis. The specific lesions and/or organs incorrectly classified must be categorized for the false negative understaged patients.

Source documents for all standard diagnostic modalities reports must be submitted. Confirmation of positive NR-LU-10 findings that are not contained in the standard diagnostic modality reports must be supported by source documents.

Patients entered into the Phase III trial that are listed as "lost to follow up", "inevaluable" and "early termination" must be reviewed and categorized in the reanalysis.

The 89 evaluable patients that have been submitted is a very limited study size. 77 additional patients were imaged in this clinical trial that have not been submitted with complete or audited clinical data. The clinical trial findings for these patients should be fully audited and included in the reanalysis.

It is noted in the current data set from the submission that the detection of metastatic disease in the brain and extrahepatic abdomen is very low (sensitivity in brain of 25% and in abdomen of 7%). The reanalysis must address the need for standard diagnostic modalities to support NR-LU-10.

DATE: December 11, 1995

FROM: George Mills, M.D., Co-Chairperson, PLA Committee

Thomas Bull, Ph.D., Co-Chairperson, PLA Committee

SUBJECT: **Review of Deficiencies in Clinical Information and Data of September 22, 1995, Sponsor Response to Deficiencies**

TO: PLA Committee, PLA 94-0308

Three deficiencies in clinical information and data were identified in CBER's letter of September 22, 1995. The sponsor has successfully responded to all deficiencies to complete the PLA file as requested.

The first deficiency listed the lack of a fully blinded interpretation of the 99mTc-NR-LU-10 Fab images. The sponsor has provided the fully blinded interpretation data (R-2) for review.

The second deficiency listed was the incomplete submission of all patient images. The sponsor had previously agree to submit all images but the complete submission of all images was not provided as of September 22, 1995. The sponsor has provided all images for all patients.

The third deficiency listed the incomplete submission of the source documents. The sponsor has provided all available source document.

CBER - Biological Approvals

Biological Device Application Approvals

Tradename	Description and Indication for Device	Applicant	Approval Date
PPIS Ver. 2.0	Blood establishment computer software	Bayer Corporation 800 Dwight Way Berkeley, CA 94701-1986	08/07/98
Abbott DMS II Data Management System	Blood establishment computer software	Abbott Laboratories 100 Abbott Park Road Abbott Park, IL 60064-3500	08/12/98

MEMORANDUM

date: Aug. 26, 1994
from: Ira Berkower, M.D., Ph.D., Lab of Immunoreg., DAPP
to: T. E. Bull, Ph.D., Co-Chairman, Nr-Lu-10 Committee
re: PLA 94-0308 NrLu10 monoclonal Ab for imaging

I have reviewed the volumes concerning imaging of small cell lung cancer with the Tc99 labeled monoclonal antibody and the equivalence of the monoclonal antibody being made by Thomae with that made previously by ———— I have the following comments:

A. Imaging small cell lung cancer.
1. Sensitivity: Overall, the monoclonal antibody works quite well. A good measure of usefulness is whether the monoclonal antibody can image those organs which are most commonly affected by the tumor. As shown in the accompanying table, the monoclonal detects 74% or greater of the metastases to lung, bone, marrow, mediastinal lymph nodes, liver, and lymph nodes in the neck. It also detected 60% of metastases involving the pleura. It does poorly (33% or less) on brain, abdomen, and abdominal lymph nodes. Taken together, the organs that are well visualized represent about 90 % of all organs containing metastatic tumors, while the poorly visualized organs represent only 10% of the tumors. This is good sensitivity for this type of test.

Organ	Detected/Involved	Total	% Detected
Lung	73/79		92
Mediastinal LN	44/50		88
Liver	20/27		74
Bone	21/26		81
Neck & Axillary LN	21/24	238	88
Bone Marrow	13/17		76
Pleural Effusion	5/9		56
Pleural Mass	4/6		67
Brain	4/12		33
Abdomen	1/10	28	10
Abdominal LN	0/4		0
Spleen	0/2		0

The size of the lesion is another factor affecting sensitivity, as shown below.

Size	Detected/Total	% Detected
< 1 cm	15/48	31
1- 3 cm	156/278	56
> 3 cm	164/181	91

Again, the important thing is that most lesions are 1 cm or larger by the time they cause symptoms or are detectable by routine tests. If smaller lesions could be detected routinely, this would be a major advance.

2. Comparison with other tests. Detection of involved organs is compared for NrLu10 vs. the other tests.

		Std Tests +	Std Tests -
NrLu10	+	196	38
	-	57	

Compared with the standard tests, NrLu10 detected 38 additional organs, but missed 57. Of the 38 organs detected by NrLu10 only, 12 were confirmed subsequently. Because of the 57 organs missed, however, additional diagnostic tests are needed when the NrLu10 scan is negative.

3. Specificity. There were very few false positive images, and the positive predictive value is >95%. Once a positive scan is obtained, no further workup is needed for staging.

B. Intended use. I suggest that clinical efficacy should be based on the first image, consistent with their indication "for primary staging of small cell lung cancer". A negative test would be followed by other tests from the standard battery.

Follow up imaging should be pursued later as a second indication. This is consistent with CBER policy, and it also makes sense. Once a lesion is found by NrLu10, later followup tests could be directed at this anatomical site, without doing unnecessary tests. For example, a positive scan for liver metastases could be followed up by abdominal CAT scan or liver scan. Some routine tests could be omitted altogether, such as bone scan, while others should still be done, such as a CAT scan of the brain.

C. Human anti-mouse immunoglobulin. One worry with mouse monoclonals is the development of human antibodies against the monoclonal, which could cause allergic reactions or prevent subsequent imaging with the same monoclonal or others.

By converting NrLu10 to F(ab')2 fragments, it was hoped that immunogenicity would be reduced. During the phase I/II trials, NrLu10 was given both as intact IgG and as Fab fragment. When IgG was given, 5 out of 7 patients developed antibodies. When Fab only was given, 5 out of 48 patients developed antibodies.

During the phase III trial, 53 patients received Fab only, and only 3 developed antibodies. The anti-mouse antibodies developed 6 to 9 weeks after a single injection of antibody. They included lots of antibodies directed against the variable region of NrLu10, so-called anti-idiotype. This is common with mouse monoclonals and was also observed with the intact IgG monoclonal OK-T3, in a higher percentage of patients and after a shorter

time (10 days to 2 weeks).

It appears that using the Fab fragment paid off, and the low incidence of human anti-mouse IgG antibodies is one result. This may indicate a safer product, and it also suggests that second imaging may be possible. Although this was good immunochemistry back in 1988, it is now possible to make antibodies even more "humanized", by such tricks as grafting the hypervariable or contact residues of the V region onto the framework of a normal human antibody. However, I think this Fab is quite good.

It has the additional advantages of rapid escape from the circulation and entry into the tumor, as well as a short biological half life that matches the physical half life of the radiolabel. As recommended in the points to consider, this is the ideal combination for imaging, and gives the lowest radiation dose to the patient.

D. Safety.

1. Thyroid function. Since it is known that the monoclonal binds normal thyroid tissue, I have looked for evidence of thyroid toxicity. In item 5.6, Vol. 15, p. 24, they state that "None of the evaluable patients had clinically significant changes in thyroid function", with respect to 53 of the 96 patients in the phase III trial. In contrast, in item 5.3.1, Vol 13, p. 215C, table 2 shows that thyroid abnormalities were observed in several of the 515 total patients receiving Nr-Lu-10 during other trials, including 2 possibly related to the antibody, 5 remotely related, 17 not related, and 1 uncertain in the opinion of the clinician. I cannot find the actual thyroid test results for these 7 possible or remote patients.

A second question was whether thyroid injury might occur in the first three days after injection, rather than at the three week timepoint chosen. I have looked at eight random cases in Vol. 19 and found two of eight with thyroid function tests on the day after injection. Both were normal. To rule out unexpected effects on the thyroid, I suggest the following:

a. A table listing all thyroid function tests performed on all 515 patients.

b. For the 7 patients referred to as possibly or remotely related in item 5.3.1: clinical data, including why they were not considered to be caused by the monoclonal.

c. A table showing all thyroid test values obtained in the first three days after injection.

There is no evidence of harm from antibody binding to normal thyroid tissue, and these data could help us to lay this issue to rest.

2. Other organs. Salivary glands & pancreas.

The salivary glands are imaged, and the pancreas does show chemical evidence of injury in 10 to 13% of patients, manifested by amylase and lipase elevations. But there was no evidence of pancreatitis or sialadenitis, and I consider the findings to be of minor significance.

3. Allergic reactions. There were two allergic reactions, one occurring in Phase II and one in the Phase III trial. Both involved urticaria, starting 3 to 6 hours after a dose, and both were in patients with a history of drug allergy. Neither was life threatening, but any systemic allergy should be taken seriously. Generally, mouse monoclonals are well tolerated in people, and the Fab fragment used here may be even safer. I suggest allergy precautions should be observed with each dose, particularly having trained personnel in attendance and the patient observed continuously for 15 minutes, and regularly for the next 6 hours after a dose.

E. Equivalence. Equivalence between the old material produced at [redacted] and the new material produced at Thomae was demonstrated biochemically, immunologically, and clinically.

1. Biochemical equivalence was shown by size-exclusion HPLC, SDS PAGE gels, isoelectric focusing, and tryptic peptides. The tryptic map was a particularly sensitive test, and showed good evidence of equivalence.

2. Immunological equivalence was shown by recloning the producer line for NrLu10 and showing that all IgG producing cells were making immunoreactive NrLu10. In addition, they showed equivalent binding to a variety of tumor cell extracts, including colorectal CA, breast,, and small cell lung CA (HUT-146 and SHT-1), but not T cell or B cell tumors, myeloma, or melanoma tumor lines. Immunohistology showed equal binding to a variety of normal tissues (thyroid, kidney and colon) but not others (spleen). The Tc99 labeling kit worked well with either source of monoclonal. ELISA immunoreactivity of the new lots was better than their standard by 1.29 to 1.42 fold, comparable to or better than their earlier lots.

3. Biological equivalence was shown by biodistribution in mouse tissues and clearance of labeled monoclonal antibody from the blood of these animals.

4. Clinical equivalence was shown by two studies 9205 and 9301. In 9301, five patients with non-SCLC were imaged sequentially on different days with old and new lots of NrLu10. Blood clearance and biodistribution were the same for both. Tumor imaging was compared. Two patients at VMM site had nine lesions, but none were imaged by either preparation of NrLu10. Three patients at the UWA site had 14 lesions, of which one reviewer called 5 positive and the other called 7 positive by scan. The second reviewer called both monoclonals the same for every lesion. The first reviewer rated the new material as better on two lesions, the same on two, and worse on one. There was only one lesion that was seen by the old and not by the new material.

In study 9205, eight patients with SCLC (the proposed indication) were imaged by the new (Thomae) monoclonal. Four had extensive

disease and four limited disease. Imaging of involved organs with the new monoclonal closely paralleled the results in Table I above. Thus, a high percentage of involved organs were detected correctly for metastases to lung, liver, neck and axillary LN, mediastinal LN, and pleura, as were half of bone metastases, but 3 out of 4 brain lesions were missed. All eight patients were staged correctly, including one who was downstaged from extensive to limited disease by NrLu10. The patients with extensive disease all had multiple positive lesions detected by NrLu10. This study shows that the Thomae material is clearly capable of detecting metastatic lesions for correct staging of patients with small cell lung cancer.

MEMORANDUM

Date: July 24, 1995
From: Ira Berkower, M.D., Ph.D., Lab of Immunoreg. DAPP
To: Tom E. Bull, Ph.D., Co-chair, PLA Committee
Re: PLA for NrLu10/ [redacted]

In response to our letter of Dec. 27, 1994, the sponsors have prepared thoughtful and quite thorough answers. We now have virtually all of the information we need for approvability.

Taking each question individually:

1. Blinded reviewers. In the clinical trial, the first reviewer made a diagram of all the known lesions before reading the NrLu10 images, while the second reviewer read them blind. If they disagreed, a third reviewer read the images blind, although he was then allowed to discuss them with the other reviewers. The consensus of two reviewers gave the final reading.

Although this design was approved by FDA before and after the study, our committee wanted to be sure that the positive results with NrLu10 did not somehow depend on the prior conventional tests. Some of these tests will probably not be done if NrLu10 becomes widely available.

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In summary, the unblinded first reviewer helped reach a positive diagnosis in a few cases, but the blinded second reviewer was also capable of detecting metastases in the vast majority of cases without other clinical data. In addition, the high PPV was maintained, despite blinding.

The real clinical results will probably lie somewhere in between. Every patient will have a chest X ray, but few will have a bone or liver scan before this procedure. Thus, I expect the clinical results will be in between the two tables reported above.

2. Previously unsuspected lesions detected by NrLu-10.

Of 95 new lesions identified by NrLu-10, 34 were subsequently confirmed and 61 remained uncertain. Of the confirmed lesions, (see Table 16 attached) the most common were in bone (21), and some were in lymph nodes, including supraclavicular, mediastinal, and axillary/cervical. These nodes are frequently metastasized and are not specifically imaged by the standard tests.

Of the unconfirmed lesions, many were also to bone and lymph nodes, and I suspect they are correct. The bone lesions were often found in patients with multiple other metastatic lesions. Two cases that were upgraded by NrLu10 are described in [redacted]

3. False positive lesions and organs: there was only one, coming from the thyroid.

False negative lesions and organs: As was shown previously, the NrLu-10 scan does miss some lesions. A summary showed that half of the patients (45 out of 89) had at least one involved organ missed. However, this rarely changed the clinical stage, indicating that other metastases were usually detected in the same patient.

4. Patients whose NrLu-10 stage differed from the standard stage:

a. One patient was downgraded to limited stage, based on NrLu-10, but in fact, both tests had difficulty evaluating his liver. I would call it a tie in the gray zone.

b. The three possible false positives by NrLu-10 all seem just as likely to be true positives for organ involvement.

c. The four upgrades to extensive disease are important. One patient [redacted] was confirmed when the doctors attempted surgery

based on limited disease by the standard workup, despite a positive NrLu-10 scan for mediastinal nodes. The nodes were removed surgically, and the diagnosis was confirmed by biopsy; the rest of the procedure had to be canceled. In another case, [redacted] NrLu-10 picked up bone mets that were missed by standard bone scan, but later confirmed by MRI.

Conclusion: certain discrepant lesions, particularly involving bone and lymph nodes, are likely to be decided in favor of NrLu-10.

d. False negative NrLu-10 images, due to missed lesions and organs, have been found in every analysis. For this reason, negative studies must be followed up by CT scan of brain and abdomen.

5. Seven patients were not evaluated, some due to change in pathologic diagnosis to a different cancer (4 patients). Five others stopped the study early, before HAMA were completed, but all images were done, so they were counted in the study.

7. In those cases where NrLu-10 stage agreed with standard stage, they do not have all the reports of the standard test results. But in all cases where they differ, the reports are in. This seems adequate to me. When both agree, what is the point of obtaining further data?

8. The package insert will have to include a table showing poor imaging of brain and abdomen (non-hepatic lesions).

9. Thyroid function tests. Fifty two patients were evaluated before and 3 weeks after imaging. Four had abnormal thyroid function tests, but three could be explained by other means. Both of the patients with low T4 and high TSH were on synthroid replacement therapy prior to imaging. This illustrates the fact that we often undertreat these patients.

Of the two patients with high T4 and low TSH, one had a history of hyperthyroidism treated with radioiodine and synthroid replacement.

Only one patient, [redacted] had unexplained hyperthyroidism after imaging. However, the baseline T4 was just at the upper

limit of normal, and I suspect this is just a minor deviation above normal level for this patient.

In summary, I see no evidence for thyroid damage at three weeks following imaging. In addition, 12 patients studied at 3 days after imaging all had normal thyroid function. Thus, there is no evidence of thyroid toxicity shortly after imaging or after three weeks.

Conclusions:

A. NrLu-10 imaging by a blinded second reviewer gives nearly as good a detection rate and the same low level of false positives as was reported previously for a consensus review. I expect the future performance to be somewhere in between these two results.

B. Many of the newly diagnosed lesions were confirmed, and many of the unconfirmed new lesions were in the same organs, suggesting that they may also be true positives.

C. Patients with discrepant staging were examined extensively, and the conclusions are the same as before: excellent PPV, but only fair NPV. Good images are obtained for the organs which receive about 80% of all metastases, but other organs are not well imaged. Several patients were correctly staged as extensive disease by NrLu-10, although they were not staged correctly by standard tests.

D. The unaudited cases do not change the findings of safety and efficacy, [redacted]

E. No evidence of thyroid toxicity was detected.

Table 16

Listing of 34 previously unsuspected lesions that are True SCLC and that were first detected in NR-LU-10 images, either by the Second Reviewer (Rev2) or the Final Blinded Interpretation (Final Bl.) (pleural effusions not included).

Patient	Lesion	Detected by		Organ	Corroborating Standard Modality
		Rev2	Final Bl.		
	C	Y	Y	Bone	Bone Scan
	B	Y	Y	Ax./Cerv. LN	Physical Exam
	AA	Y	Y	Bone	Bone Scan
	DD			Bone	Bone Scan
	A	Y	Y	Sup. Cl. LN	Physical Exam
	A	Y	Y	Bone Marrow	Biopsy
	B	Y	Y	Breast	X-Ray
	AA	Y	Y	Bone	Bone Scan
	D	Y	Y	Bone	Bone Scan
	F	Y	Y	Bone	Bone Scan
	BB	Y	Y	Bone	Bone Scan
	P	Y	Y	Mediast. LN	CT
	Q			Mediast. LN	CT
	B	Y	Y	Lung	CT
	C			Mediast. LN	CT
	A	Y	Y	Bone	Bone Scan
	AA	Y	Y	Bone	Bone Scan
	BB	Y	Y	Bone	Bone Scan
	CC	Y	Y	Bone	Bone Scan
	A	Y	Y	Lung	Bone Scan
	A	Y	Y	Lung	CT
	C	Y	Y	Bone	Bone Scan
	EE			Bone	Bone Scan
	CC	Y	Y	Bone	CT
	AA	Y	Y	Lung	CT
	A	Y	Y	Brain	CT
	AA	Y	Y	Lung	CT
	B	Y	Y	Bone	Bone Scan
	CC	Y	Y	Bone	Bone Scan
	C	N	Y	Bone	CT
	A	N	Y	Ax./Cerv. LN	CT
	A	N	Y	Lung	X-Ray
	B	N	Y	Other - Thorax	CT
	A	N	Y	Mediast. LN	Biopsy